



NOTES

NEUROMUSCULAR JUNCTION DISEASES

GENERALLY, WHAT ARE THEY?

PATHOLOGY & CAUSES

- Disorders impairing neuromuscular transmission lead to muscle fatigability, weakness

CAUSES

- Autoantibody production
 - Targeted against neuromuscular transmission pathway proteins
- Myasthenia gravis (MG)
- Lambert–Eaton myasthenic syndrome (LEMS)
- Transient acquired neonatal myasthenia
- Genetic mutation
 - Affecting pathway components (e.g., congenital myasthenia)

COMPLICATIONS

- Respiratory muscles involved → potentially fatal respiratory failure

SIGNS & SYMPTOMS

- Primary clinical manifestation
 - Painless muscle weakness without significant muscle atrophy
 - Ocular, extraocular, oropharyngeal, bulbar, neck, limb, respiratory muscles

DIAGNOSIS

DIAGNOSTIC IMAGING

CT scan

- Thymoma (MG)
- Small-cell lung carcinoma (LEMS)

LAB RESULTS

- Serologic test for specific antibodies

OTHER DIAGNOSTICS

Electrophysiologic study

- Repetitive nerve stimulation
 - Decremental response/improvement
- Electromyogram
 - ↓ muscle action potential

Pulmonary function test (PFT)

- Periodically
 - Detect respiratory muscle involvement in forced vital capacity (FVC) ↓

TREATMENT

- Treat underlying cause (e.g. LEMS malignancy)

MEDICATIONS

- Acetylcholinesterase inhibitors
 - Inhibit acetylcholine degradation → ↑ acetylcholine concentration in neuromuscular junction (symptomatic therapy)
- Immunomodulating agents
 - ↓ autoantibody production
 - Individuals with poor acetylcholinesterase inhibitor response
 - Corticosteroids/other immunosuppressive agents
- If above fails/emergency (e.g., myasthenic crisis)
 - Plasmapheresis/intravenous immunoglobulin (IVIG)

VISIT...

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LAMBERT–EATON MYASTHENIC SYNDROME (LEMS)

osms.it/lambert-eaton-myasthenic

PATHOLOGY & CAUSES

- Rare autoimmune disorder
 - Autoantibodies **inhibit presynaptic calcium channels** on motor neurons → reduced acetylcholine release in neuromuscular junction
- Muscle weakness
 - Improves temporarily after **repeated muscle use** (no significant muscle atrophy)
- Mostly affects somatic nervous system, can also affect autonomic nervous system's parasympathetic part
- Middle-aged adults (most cases)

CAUSES

Type II hypersensitivity reaction

- B cells produce **antibodies** that target, **block voltage-gated calcium channels** located presynaptically on motor neurons → only few unbound channels available to open, allow calcium in → ↓ calcium within neuron (insufficient to trigger acetylcholine release) → ↓ acetylcholine release in neuromuscular junction → attached muscle fiber does not contract
- **Repeated stimulation** by brain's electrical impulses → enough calcium might get through remaining unbound calcium channels → acetylcholine release → muscle contraction

RISK FACTORS

- Malignancy
 - Strong **small-cell lung cancer** association; stimulus for antibody production is same calcium channel expression in neoplastic cells
 - Other associated malignancies include

lymphoproliferative disorders (e.g., Hodgkin's lymphoma)

- Autoimmune diseases
 - Hashimoto's thyroiditis, diabetes mellitus type 1, vitiligo

COMPLICATIONS

- Respiratory muscle involvement → **respiratory failure**
- Underlying malignancy → can lead to death

SIGNS & SYMPTOMS

- Progressive, **symmetrical proximal muscle weakness** (e.g., shoulders, hips, thighs) → difficulty climbing stairs/standing when seated
 - **Paraneoplastic LEMS**: more rapidly progressive course
- Warming-up phenomenon
 - Repeated muscle use → weakness temporarily relieved
- Reflex strength ↓
 - Muscle activation → reflex recovery/improvement
- Small minority
 - Ocular, oropharyngeal muscle involvement
- Advanced stages
 - Possible respiratory muscles involvement → respiratory failure (myasthenic crisis)
- Autonomic symptoms
 - Dry mouth (most common), constipation, blurry vision, erectile dysfunction, urinary problems, syncope

DIAGNOSIS

DIAGNOSTIC IMAGING

CT scan

- Chest
 - Detect underlying small-cell lung cancer
- Abdomen, pelvis also recommended
- Negative initial malignancy evaluation
 - Periodical screening recommended

LAB RESULTS

- Serological tests
 - Detect **antibodies** against the voltage-gated calcium channels

OTHER DIAGNOSTICS

- Electrophysiologic studies
 - **Repetitive nerve stimulation**: ↑ muscle action potential amplitude
 - **Electromyogram**: ↑ muscle action potential amplitude after exercise
- PFT
 - ↓ FVC → respiratory muscle involvement

TREATMENT

MEDICATIONS

- Symptomatic therapy
 - **Acetylcholinesterase inhibitors**: minimal effect
 - **Aminopyridines**: block potassium channels → **prolonged nerve membrane depolarization** → ↑ calcium entry → ↑ acetylcholine release in neuromuscular junction
- If above methods fail
 - Immunomodulating agents can be used (corticosteroids, other immunosuppressive agents)

OTHER INTERVENTIONS

- Occasionally treated with IVIG/plasmapheresis
 - More severe cases

MYASTHENIA GRAVIS

osms.it/myasthenia-gravis

PATHOLOGY & CAUSES

- Autoimmune disorder; significant skeletal muscle weakness
 - Decreased acetylcholine receptor function → **worsens with muscle use**
 - Most common neuromuscular junction disorder
- Type II hypersensitivity reaction
 - B cells produce **antibodies against postsynaptic nicotinic acetylcholine receptors** of neuromuscular junction/receptor-associated proteins
 - Autoantibodies targeted against muscle-specific receptor tyrosine kinase (MuSK) → ↓ in acetylcholine receptor function
- Acetylcholine **cannot bind** → normal action potentials cannot be generated (adjacent muscle)
- Complement activated → inflammatory response initiation → postsynaptic membrane damage → acetylcholine receptor destruction
- Bimodal onset age
 - 20–30 years old (biologically-female predominance)
 - 60–70 years old (biologically-male predominance)
- Associated with thymic abnormality; thymus considered antigen source

promoting autoantibody production (most cases)

- Neonatal myasthenia gravis
 - Transient myasthenia form (newborn from individual with myasthenia gravis)
 - Maternal antibodies → transplacental passage → neuromuscular junction function interference
- Rare non-immune mediated forms
 - E.g. congenital myasthenia gravis
 - Mutations affecting neuromuscular transmission

COMPLICATIONS

- Myasthenic crisis
 - Decreased respiratory muscle function → life-threatening respiratory failure (requires mechanical ventilation)
 - Occurs spontaneously/precipitated (e.g. surgery, infection, medication, immunosuppressive-agent withdrawal)

SIGNS & SYMPTOMS

- Fluctuating muscle weakness
 - Exacerbated by repetitive muscle use throughout day/after exertion/repetitive movement
- Improves with rest
- Progression
 - Symptoms continuously present, fluctuate from mild–severe
- Sensation, reflexes preserved

Clinical MG forms

- Ocular myasthenia
 - Limited (eyelid, extraocular muscle); individuals (50%) with ocular myasthenia will → generalized myasthenia (< two years)
- Generalized myasthenia
 - Ocular, bulbar, facial, limb, respiratory muscle
- Ocular muscles
 - Eyelid (ptosis), extraocular (binocular diplopia)
- Bulbar muscle
 - Jaw closure (prolonged chewing → weakness), oropharyngeal (dysarthria,

dysphagia), palatal (nasal tone, prolonged speech → hypophonia)

- Facial muscle
 - Facial weakness, facial expression loss
- Neck muscle
 - Cannot keep head up (“drooped head syndrome”)
- Limb muscle
 - Proximal, asymmetric muscle weakness
- Respiratory muscle
 - Respiratory failure (myasthenic crisis)

DIAGNOSIS

DIAGNOSTIC IMAGING

CT scan

- Chest scan to detect associated thymic abnormalities
 - Abnormal thymus (most cases)
 - Thymoma

LAB RESULTS

- Serologic test
 - Acetylcholine receptor antibodies (AChR-Abs)/muscle-specific receptor tyrosine kinase antibodies (MuSK-Abs)
 - Most specific tests
 - Seronegative for AChR-Abs, MuSK-Abs

OTHER DIAGNOSTICS

- Electrophysiologic studies
 - Repetitive nerve stimulation studies: progressive decline in muscle action potential amplitude (decremental response)
 - Single-fiber electromyography: increased jitter
- Tensilon test
 - Edrophonium: acetylcholinesterase inhibitor with rapid onset, short acting duration
 - Prolongs acetylcholine presence in neuromuscular junction → marked improvement
 - Easy to perform/limited utility; high false-positive rate, possible complications from muscarinic effects

(especially older adults, e.g. bradycardia, bronchospasm)

- PFTs
 - Periodical FVC monitoring; FVC ↓ reveals respiratory muscle involvement
- Ice pack test
 - Ice pack application (2–5 minutes) → MG-affected muscles
 - Neuromuscular transmission improvement in low temperature

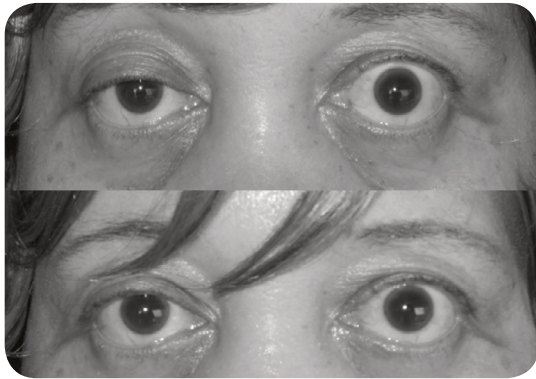


Figure 85.1 A biologically-female individual with myasthenia gravis demonstrating ptosis of the right eye before treatment (above) and after treatment (below) with edrophonium.

TREATMENT

- No curative method

MEDICATIONS

- Avoid MG-exacerbating drugs (e.g. aminoglycosides, tetracyclines, beta-blockers, quinidine)
- Acetylcholinesterase inhibitors
 - Symptomatic therapy
- Immunomodulating agents ↓ autoantibody production
 - Individuals with poor acetylcholinesterase inhibitor response
- Corticosteroids, other immunosuppressive agents

SURGERY

- Thymectomy, especially for thymoma; myasthenia often improves/disappears
- Rapidly worsening myasthenia/myasthenic crisis
 - Intubation
 - Plasmapheresis/intravenous immunoglobulin (IVIG)
 - Long-acting immunotherapy (e.g., corticosteroids, azathioprine)



MNEMONIC

Edrophonium vs. pyridostigmine

eDrophonium for Diagnosis
pyRIDostigmine is to get RID of symptoms